(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/74784 A1

(51) International Patent Classification[7]: A61P 3/04, 25/18, A61K 45/06, 31/55, 31/505, 31/495, 31/445

(21) International Application Number: PCT/US00/09811

(22) International Filing Date: 22 May 2000 (22.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/138,315 9 June 1999 (09.06.1999) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **TODD, Jane, Rogers** [US/US]; 503 Seaton Springs Court, Louisville, KY 40222 (US).

(74) Agents: **PALMBERG, Arleen** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/74784 A1

(54) Title: COMBINATION FOR TREATING WEIGHT GAIN ASSOCIATED WITH ANTIPSYCHOTIC USE COMPRISING AN ATYPICAL ANTIPSYCHOTIC AND AN H2 ANTAGONIST

(57) Abstract: The invention provides methods and compositions for the prevention and treatment of weight gain associated with antipsychotic use. These methods and compositions employ a compound having activity as an atypical antipsychotic and an H2 antagonist.

COMBINATION FOR TREATING WEIGHT GAIN ASSOCIATED WITH ANTIPSYCHOTIC USE COMPRISING AN ATYPICAL ANTIPSYCHOTIC AND AN H2 AN

The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides methods and compositions for treating weight gain associated with the use of antipsychotics.

Psychoses are serious mental illnesses characterized by defective or lost contact with reality. Psychotic patients may also suffer hallucinations and delusions as part of their disease. Psychoses exact a tremendous emotional and economic toll on the patients, their families, and society as a whole. While the mechanisms underlying these diverse disease states are poorly understood, recently discovered therapies are offering new hope for the treatment of psychotic patients. Progress in the treatment of psychotic conditions has been achieved through the introduction of new, atypical antipsychotic agents.

Antipsychotic use has been shown to be effective in treating schizophrenia, schizoaffective disorders and other related conditions. While the side effect profile of these atypical antipsychotics is far superior to that of traditional agents, weight gain is a side effect that has been observed in patients treated with these agents. Clinical experience and published studies indicate that atypical antipsychotic use may be associated with marked weight gain; significant weight gain is seen in approximately 50% of adolescent patients. Patients who gain weight when prescribed an antipsychotic are more likely to discontinue the drug because of weight gain.

Therefore excessive weight gain associated with antipsychotic use is a significant issue given its impact on compliance, general health and psychological issues.

Histamine-2 (H-2) antagonists reversibly bind to the histamine receptors on the basolateral membrane of parietal cells, blocking stimulation by the histamine that is released form tissue mast cells and enterochromaffin-like cells. As a result, basal and food stimlulated gastric acid secretion are inhibited and intragastric pH is raised (Gilbert G., Chan CH, and Thomas E: Peptic ulcer disease: How to treat it. Postgrad Med 1991; 89:91-98.)

The invention provides a method for treating a patient suffering from or susceptible to weight gain associated with the use of antipsychotics, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is an H2-antagonist.

The invention further provides the use of an effective amount of an a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is an H_2 antagonist for the manufacture of a medicament for the treatment of a patient suffering from or susceptible to weight gain associated with the use of anti-psychotics.

The invention also provides a pharmaceutical composition which comprises a first component which is an atypical anti-psychotic, and a second component which is a H2 antagonist.

In another embodiment the invention provides a pharmaceutical composition adapted for the treatment of a patient suffering from or susceptible to weight gain associated with the use of an antipsychotic, comprising as the active ingredients a combination of an atypical antipsychotic and an H_2-antagonist.

In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

The Compounds

In the general expressions of the present invention, the first component is a compound which acts as an atypical antipsychotic. The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al.,

Neuropsychopharmacology, **14**(2), 111-123 , (1996)). Atypical antipsychotics include, but are not limited to:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety;

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Patent No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., **24**, 62 (1988));

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663, which is herein incorporated by reference in its entirety;

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety;

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of

schizophrenia are described in U.S. Patent No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; and

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031. U.S. Patent Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety.

Similarly, when the invention is regarded in its broadest sense, the second component compound is an H2 antagonist. H2 antagonists include, but are not limited to:

Cimetidine, N"-cyano-N-methyl-N'-[2-[[(5-methyl-1-H-imidazol-4-yl)methyl]thio]-ethyl]-guanidine is marketed as the hydrochloride salt. The compound is described in U.S. Patent No. 3,950,333.

Ranitidine, N[2-[[[5-{dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine is marketed as the hydrochloride salt. The compound is described U.S. Patent No. 4,521,431.

Famotidine, N'-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide is marketed as the free base. The compound is described in U.S. Patent No. 4,283,408.

Nizatidine, N-[2-[[[2-[(dimethylamino)methyl]-4-thizaolyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine is marketed as the free base. The compound is described in U.S. Patent No. 4,375,547.

Roxatidine, 2-hydroxy-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]acetamide acetate is investigational in the U.S. NDA discontinued for roxatidine. The compound is described in U.S. Patent 5,221,688.

Ebrotidine, 4-bromo-N-[[[2-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]ethyl]amino]methylene]benzenesulfonamide is described in U.S. Patent No. 4,728,655.

Niperotidine, N-(1,3-benzodioxol-5-ylmethyl)-N'-[2-[[[5-[(dimethylamino)methyl}-2-furanyl]methyl]thio]ethyl]-2-nitro-1,1-ethenediamine is described in U.S. patent No. 5,030,738.

Lafutidine,(Z)-2-[(2-furanylmethyl)sulfinyl]-N-[4-[[4-(1-piperidinylmethyl)-2-pyridinyl]oxy]-2-butenyl]-acetamide is described in U.S. Patent No. 4,912,101.

2-(N-pentyl-N-guanidino)-4-(2-methylimidazol-4-yl)thiazole is described in U.S. Patent No. 4,560,690.

2-(4-hydroxybenzoyl)benzoic acid with 2-[(2-hydroxyethyl)thio]-N-[3-[3-9]-piperidinylmethyl)phenoxy]propyl]acetamide (1:1) is described in U.S. Patent No. 5,192,774.

Osutidine, (E)-N-[[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino][[2-[[[5-[(methylamino)methyl]-2-furanyl]methyl]thio]ethyl]amino]methylene methanesulphonamide is described in JP 09221422, JP 03251527.

Pibutidine, (Z)-3-amino-4-[[4-[[4-(1-piperidinylmethyl)-2-pyridinyl]oxy]-2-butenyl]amino]-3-cyclobutene-1,2-dione monohydrochloride is described in JP 05065226, JP 03251571 and JP 2858941.

Etintidine, N-cyano-N'-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]-N''-2-propynyl-guanidine is described in U.S. Patent No. 4,339,439. The combination of etintidine and pepstatin lowers the amount of etintidine needed and therefore reduces side effects.

4-[3-(benzo-1,3-dioxol-5-yl)thioureido]-N-[3-[3-(piperidinomethyl)phenoxy]propyl]butyramide is described in EP 531228.

[4-[[[2-[5-[3-(diethylamino)propyl]-1,4-dihydro-6-methyl-4-oxo-2-pyrimidinyl]ethyl]thio]methyl-2-thiazolyl]guanidine trihydrochloride is described in EP 86647.

Tiotidine, N-[2-[[[2-[(aminoiminomethyl)amino-4-thiazolyl]methyl]thio]ethyl]-N'-cyano-N''-methyl-guandine is described in U.S. Patent 4,165,377.

Lamitidine, 1-methyl-N5-[3-[3-[(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-3,5-diamine is described in U.S. Patent No. 4,318,913.

Zaltidine,[4-(-methyl-1H-imidazol-4-yl)-2-thiazolyl]-guanidine is described in U.S. Patent 4,374,843.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

It will be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single H2 antahonist as a second component compound is preferred, combinations of two or more H2-antagonists may be used as a second component if necessary or desired.

While all combinations of first and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

olanzapine/nizatadine
olanzapine/cimetidine
olanzapine/ranitidine
olanzapine/famotidine
olanzapine/roxatidine
olanzapine/ebrotidine
olanzapine/niperotidine
olanzapine/lafutidine
clozapine/ nizatadine
risperidone/ nizatadine
sertindole/ nizatadine

quetiapine/ nizatadine
ziprasidone/ nizatadine

In general, combinations and methods of treatment using olanzapine as the first component are preferred. Furthermore, combinations and methods of treatment using nizatadine as the second component are preferred. Especially preferred are combinations and methods of treatment using olanzapine as the first component and nizatadine as the second component.

It is especially preferred that when the first component is olanzapine, it will be the Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645

3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111

d
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28

3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
d	**I/I_1**
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper K_a radiation source of wavelength, l =1·541Å.

It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph.

As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content of

acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated water.

The polymorph obtainable by the process taught in the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

d
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439

5.5895
5.3055
4.9815
d
4.8333
4.7255
4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	**I/I_1**

9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
d	**I/I_1**
6.2439	5.21
5.5895	1.10
5.3055	0.95
4.9815	6.14
4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40

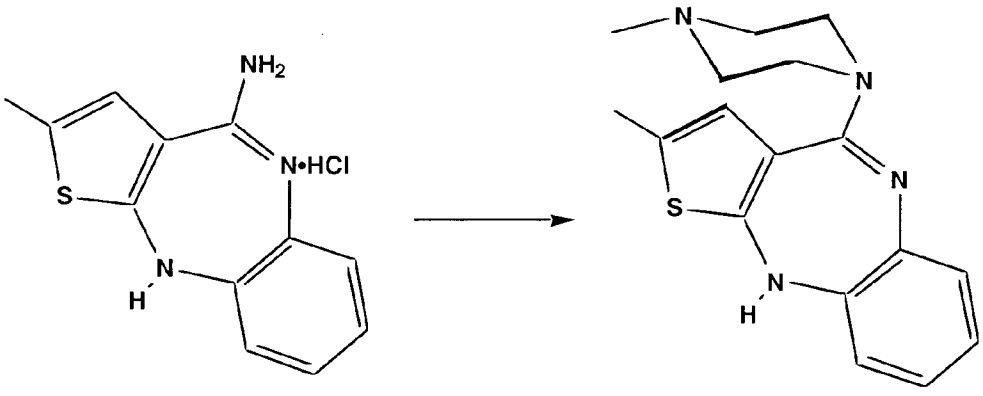
2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10
2.5956	1.73

The x-ray powder diffraction patterns herein were obtained with a copper K_a of wavelength 1 = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

Though Form II olanzapine is preferred it will be understood that as used herein, the term "olanzapine" embraces all solvate and polymorphic forms unless specifically indicated.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes
Intermediate 1 : 75 g
N-Methylpiperazine (reagent) : 6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the above-referenced '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until = 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.
Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency $\geq$ 97%, total related substances < 0.5% and an isolated yield of > 73%.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the

free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Olanzapine: from about 0.25 to 100 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;

Clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;

Risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;

Sertindole: from about .0001 to 1.0 mg/kg daily;

Quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;

Ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;

Cimetidine: from about 150 mg to 1600mg,once-four/day most preferably from about 300 mg to about 800 mg, once to four/day.

Ranitidine: from 40 mg to 1.2 g, once-four/day per day.

Famotidine: from 50 to 800 mg given once per day and or in divided doses.

Nizatidine: from 50-80 mg, three-four/day. Generally, however, the compounds of this invention are administered to humans orally in a daily dosage range of 140-800 mg. Smaller doses at more frequent intervals may also be employed. The preferred oral dosage range is about 2-5 mg/kg/day of mammalian body weight, although a dosage range of from 1-10 mg/kg/day can be used.

Roxatidine: from 75 to 500mg, once-four/daily, preferably once-twice/day.

Ebrotidine: from 400 to 800 mg once nightly.

Niperotidine: from 100 to 300 mg twice a day, preferably 230 mg twice a day.

Lafutidine: from 0.1 to 5 mg/kg, preferably 0.3 to 3 mg/kg per day.

2-(N-pentyl-N-guanidino)-4-(2-methylimidazol-4-yl)thiazole: from 0.1 to 20 mg/kg/body weight/day, preferably 0.2 to 2.5 mg/kg/day, in single or divided doses. If parental administration is desired, then these compounds can be given between about 0.1 to 1.0 mg/kg/day body weight/day.

2-(4-hydroxybenzoyl)benzoic acid with 2-[(2-hydroxyethyl)thio]-N-[3-[3-9]-piperidinylmethyl)phenoxy]propyl]acetamide (1:1): from 1 to 500 mg/kg,once-thrice/day.

Osutidine: from 0.05 to 1000mg given once or in divided doses.

Piputidine: from 3 to 40 mg.

Etinidine: from 150 to 200mg given q.i.d

Etinidine and pepstatin: In man, the preferred dosage of etinidine, is from about 50-150 mg, three-four/day (and most preferably from about 75 mg to 100 mg, three-four/day)(and most preferably four times). The preferred dosage of pepstatin in man is from about 100mg, seven/day to about 175 mg,four/day. Combination of etintidine and pepstatin lowers the amount of etintidine needed and therefore reduces side effects.

4-[3-(benzo-1,3-dioxol-5-yl)thioureido]-N-[3-[3-(piperidinomethyl)phenoxy]propyl]butyranide from: 10-2000mg, preferably 20-600mg per day for adults. The daily dose may be divided into 1-3 doses.

[4-[[[2-[5-[3-(diethylamino)propyl]-1,4-dihydro-6-methyl-4-oxo-2-pyrimidinyl]ethyl]thio]methyl-2-thiazolyl]guanidine trihydrochloride from: 100 to 800 mg, given once daily, or in divided doses.

Tiotidine: from 15 mg and 1500 mg, and preferably between 20 mg and 200 mg (for example 50 mg) or an intravenous subcutaneous or intramuscular dose of between 1.5 mg and 150 mg and preferably between 5mg and 20 mg being administered 2 to 4 times a day.

Lamitidine: from 1 to 6 doses to the total of some 5 mg to 2 g per day, preferably 5 to 500 mg per day.

Zaltidine: from 0.1 and 20 mg/kg body weight of the subject to be treated per day, preferably from about 0.2 to 2.5 mg/kg per day.

In more general terms, one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

Preferred ratios of olanzapine/nizatadine by weight include:

1/150
6/200
12.5/240
25/250
17.5/300
25/320

Patient treated for schizophrenia complained of weight gain of an effective amount of an antipsychotic and an effective amount of H_2 antagonist was prescribed. In follow-up visits patient was no longer gaining weight.

The adjunctive therapy of the present invention is carried out by administering a first component together with the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound.

Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to

formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. This enteric formulation is described in U.S. Patent No. 5,508,276, herein incorporated by reference in its entirety.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which

protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	25 mg
Nizatidine	150
Starch, dried	150
Magnesium stearate	10
Total	210 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	10
Nizatadine	200
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total	310 mg

The components are blended and compressed to form tablets each weighing 465 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Risperidone	5 mg
Nizatidine	300
Ethanol	25.75
Propellant (Chlorodifluoromethane)	22
	60.00
Total	100.75 mg

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 80 mg of active ingredient, are made as follows:

Sertindole	60 mg
Nizatidine	320 mg
Starch	30 mg
Microcrystalline cellulose	20 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	140 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl-pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

Formulation 5

Capsules, each containing 130 mg of active ingredient, are made as follows:

Quetiapine	70 mg
Nixatidine	240 mg
Starch	39 mg
Microcrystalline cellulose	39 mg
Magnesium stearate	2 mg
Total	180 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

Formulation 6

Suppositories, each containing 45 mg of active ingredient, are made as follows:

Ziprasidone	75 mg
Nizatidinede	250 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,080 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

Olanzapine	20 mg
Nizatidine	150 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion

of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Olanzapine	20 mg
Nizatidine	150 mg
Isotonic saline	1,000 ml

Benefit of the Invention

The present invention provides the advantage of treatment of schizophrenia with the atypical antipsychotics without the concomitant weight gain typically observed with such treatment, conferring a marked and unexpected benefit on the patient.

Microdialysis assays of monoamines

Sprague-Dawley rats (Harlan or Charles River) weighing 270-300 grams are surgically implanted with microdialysis probes under chloral hydrate/pentobarbital anesthesia (170 and 36 mg/kg i.p. in 30% propylene glycol, 14% ethanol) (Perry and Fuller, Effect of fluoxetine on serotonin and dopamine concentration in rat hypothalamus after administration of fluoxetine plus L-5-hydroxytryptophan, Life Sci., 50, 1683-90 (1992)). A David Kopf stereotaxic instrument is used to implant the probe unilaterally in the hypothalamus at coordinates rostral -1.5 mm, lateral -1.3 mm, and ventral -9.0 mm (Paxinos and Watson, 1986). After a 48 hour recovery

period, rats are placed in a large plastic bowl with a mounted liquid swivel system (CMA/120 system for freely moving animals, Bioanalytical Systems, West Lafayette, IN). Filtered artificial cerebrospinal fluid (CSF) (150 mM NaCl, 3.0 mM KCl, 1.7 mM CaCl2, and 0.9 mM MgCl2) is perfused through the probe at a rate of 1.0 ml/min. The output dialysate line is fitted to a tenport HPLC valve with a 20 ml loop. At the end of each 30 minute sampling period, dialysate collected in the loop is injected on an analytical column (Spherisorb 3 m ODS2, 2X150 mm, Keystone Scientific).

The method used to measure monoamines is as described by Perry and Fuller (1992). Briefly, dialysate collected in the 20 ml loop is assayed for 5-HT, NE and DA. The 20 ml injection goes onto the column with a mobile phase which resolves NE, DA, and 5-HT: 75 mM potassium acetate, 0.5 mM ethylenediaminetetraacetic acid, 1.4 mM sodium octanesulfonic acid and 8% methanol, pH 4.9. The mobile phase for the amine column is delivered with a flow programmable pump at an initial flow rate of 0.2 ml/min increasing to 0.3 ml/min at 5 min then decreasing back to 0.2 ml/min at 26 min with a total run time of 30 min. Flow programming is used to elute the 5-HT within a 25 min time period. The electrochemical detector (EG&G, Model 400) for the amine column is set at a potential of 400 mV and a sensitivity of 0.2 nA/V. Basal levels are measured for at least 90 minutes prior to drug administration. The drugs are prepared in filtered deionized water (volume 0.25-0.3 ml) for administration at the desired doses.

Clinical Trials

The efficacy of the method of the present invention in treating or preventing weight gain associated

with atypical antipsychotic use is shown in clinical trials. Patients diagnosed with weight gain associated with atypical antipsychotoc use are randomized to one of two treatment arms: (12) olanzapine (5-20 mg/day) and placebo; or (2) nizatidine plus olanzapine (150-320 mg/day and 5-20 mg/day, respectively). The efficacy of the treatment is monitored by comparing the weight, body mass index (BMI), percent body fat by impedance and waist circumference at baseline and montly thereafter for 12 weeks to assess changes in body composition.

We claim:

1. A method for treating a patient suffering from or susceptible to weight gain associated with antipsychotic use, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is an H2 antagonist.

2. The use of an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is an H2 antagonist, for the manufacture of a medicament for the treatment or prevention of weight gain associated with antipsychotic use.

3. A method of **Claims 1 or 2** where the first component is chosen from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone; and the second component is selected from the group consisting of nizatidine, cimetidine, vanitidine and famotidine.

4. A method of any one of **Claim 3** wherein the first component compound is olanzapine.

5. A method of **Claim 4** wherein the second component compound is nizatdine.

6. A method of any one of **Claims 1 to 5** where administration of the compounds is oral.

7. A method of any one of **Claims 1 to 6** wherein the ratio of olanzapine to nizatidine by weight is selected from the group consisting of 1/150, 6/200, 12.5/240, 25/250, 17.5/300 and 25/320, 5/150, 10/300, 20/150, 20/300, 10/150 and 5/300.

8. A pharmaceutical composition adapted for the treatment of a patient suffering from or susceptible to weight gain associated with antipsychotic use comprising as the active ingredients a combination of an atypical antipsychotic and an H2 antagonist.

9. A pharmaceutical composition which comprises a first component which is an atypical antipsychotic, and a second component which is an H2 antagonist.

10. A composition of **Claim 9** which comprises a first component chosen from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone, in combination with a second component chosen from the group consisting of of nizatidine, cimetidine, vanitidine and famotidine.
10.

11. A composition of **Claim 9** which is adapted for oral administration.

12. A composition of **Claim 9** wherein the first component compound is olanzapine.

13. A composition of **Claim 11** wherein the first component compound is olanzapine.

14. A composition of **Claim 11** wherein the first component compound is Form II olanzapine.

15. A composition of **Claim 9** wherein the second component compound is nizatidine.

16. A composition of either of **Claims 13 or 14** wherein the second component compound is nizatidine.

17. A composition of **Claim 11** wherein the first component compound is olanzapine in the amount of about 0.25 to about 50 mg.

18. A composition of **Claim 11** wherein the first component compound is olanzapine in the amount of about 1 to
about 30 mg.

19. A composition of **Claim 11** wherein the first component compound is olanzapine in the amount of about 1 to
about 25 mg.

20. A composition of **Claim 11** wherein the second component compound is nizatidinee in the amount of about 150 to about 320 mg.

21. A method of any one of **Claims 1 to 7** wherein the olanzapine is Form II.

22. A composition of **Claim 14** wherein the Form II olanaapine is substantially pure.

23. A method of any one of **Claims 1 to 6** wherein the first component is in the amount of about 1 to 25 mg.

24. A method of any one of **Claims 1 to 6** and **23** wherein the second component is nizatidine in the amount of about 150 to about 320mg.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 00/09811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P3/04 A61P25/18 A61K45/06 A61K31/55 A61K31/505
A61K31/495 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 44361 A (LAXDALE LIMITED) 3 August 2000 (2000-08-03) page 5, line 1-17; claims 1,16,18,19,27 page 27, line 12-27 ---	1-4,8-13
X	US 5 070 101 A (KAMINSKI RAM) 3 December 1991 (1991-12-03)	8-11
A	column 1, line 41-43; claims 1-4 column 2, line 56-58 column 4, line 11-15 column 4, line 19-23 ---	1-3,5,24
Y	EP 0 830 864 A (LILLY CO ELI) 25 March 1998 (1998-03-25) the whole document --- -/--	1-4,6, 8-14,18, 19,21-23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kanbier, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 00/09811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 00736 A (SMITHKLINE BEECHAM PLC) 23 January 1992 (1992-01-23) page 1, line 8-14 page 2-3; claims 3-8	1-4,6, 8-14,18, 19,21-23
A	EP 0 426 479 A (MCNEIL PPC INC) 8 May 1991 (1991-05-08) column 4; claims 1,3,5,7,9 column 6, line 56-58	1-3,6, 8-11
A	WO 94 05695 A (UNIV NEW YORK) 17 March 1994 (1994-03-17) page 5, line 26-35; claims 3,16,18,19 page 13, line 31-17; table 1	1-4,6, 8-13
A	MELTZER ET AL: "The Cimetidine-Induced Increase in Prolactin Secretion in Schizophrenia: Effect of Clozapine" PSYCHOPHARMACOLOGY, vol. 112, no. S1, 1993, pages S95-S104, XP000961760 page S96	1-3,8-11

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 2, 6-9, 11-15 and 17-24 relate to methods, uses and compositions involving compounds defined by reference to a desirable characteristic or property, namely as "atypical antipsychotic" and "H2 antagonist".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action and/or its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds as structurally specified in the present claims and examples, with due regard to the description and the general idea underlying the application.

Claims 3-5, 7, 10 and 16 were searched completely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 00/09811

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0044361 A	03-08-2000	NONE	
US 5070101 A	03-12-1991	US 5453428 A	26-09-1995
		US 5547969 A	20-08-1996
		US 5889033 A	30-03-1999
		US 5177081 A	05-01-1993
		US 5352688 A	04-10-1994
EP 0830864 A	25-03-1998	AU 719033 B	04-05-2000
		AU 4411297 A	14-04-1998
		BR 9711530 A	24-08-1999
		CN 1230886 A	06-10-1999
		CZ 9900987 A	15-12-1999
		NO 991381 A	22-03-1999
		PL 332481 A	13-09-1999
		WO 9811897 A	26-03-1998
		ZA 9707967 A	04-03-1999
WO 9200736 A	23-01-1992	AU 8194991 A	04-02-1992
EP 0426479 A	08-05-1991	AT 101515 T	15-03-1994
		AU 646230 B	17-02-1994
		AU 6568990 A	09-05-1991
		CA 2028746 A,C	03-05-1991
		DE 69006684 D	24-03-1994
		DE 69006684 T	09-06-1994
		ES 2057439 T	16-10-1994
		GR 90100786 A,B	17-04-1992
		IE 64953 B	20-09-1995
		IN 171746 A	26-12-1992
		JP 3206052 A	09-09-1991
		NZ 235877 A	25-09-1992
		PT 95753 A	30-09-1991
		US 5417980 A	23-05-1995
		US 5204118 A	20-04-1993
		ZA 9008775 A	29-07-1992
WO 9405695 A	17-03-1994	AU 4855393 A	29-03-1994
		US 5508384 A	16-04-1996